Criteria for Use: Drotrecogin Alfa (activated)

VHA Infectious Diseases Program Office, Pulmonary & Critical Care Field Advisory Group, and
Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

*For specific information on dosage, administration, preparation, and details regarding use, please refer to the manufacturer's package insert (**http://pi.lilly.com/us/xigris.pdf**). The package insert provides details regarding this drug as approved by the Food and Drug Administration. .*

A. Criteria for Use

Because of the potentially serious toxicity, lack of information for the wide spread use in high risk patients and the marginal effectiveness demonstrated in some of the groups in the clinical trials, VA clinicians should consider use of drotrecogin alfa (activated) only after the approval of a staff physician or fellow (must be a critical care fellow or an infectious disease / critical care / pulmonary attending). The following recommendations are provided for the use of drotrecogin alfa (activated) in VHA.

1. Patient is within 48 hours of the onset of the first sepsis induced organ dysfunction.

AND

2. Patient is receiving continuous monitoring in the intensive care unit. In general, it is not necessary to begin this medication in the Emergency Room, unless uncontrollable delays are expected to occur prior to movement of the patient to the intensive care setting.

AND

3. Patient has confirmed or suspected infection (positive blood culture, perforated viscus, etc.)

AND

4. Possible sepsis syndrome (modified systemic inflammatory response syndrome-(SIRS), with any 3 of the following signs:

    a. Temperature ≥ 100.4 (38° C) or ≤ 96.8 (36° C)
    b. Heart rate ≥ 90 BPM
    c. Respiratory rate ≥ 20/min or Pa CO_2 < 32mm Hg or the use of mechanical ventilation (not chronic)
    d. WBC ≥ 12,000 or ≤ 4,000 or > 10% immature neutrophils

AND

4. Acute end organ dysfunction (any two of the following five systems):

   a. CARDIOVASCULAR

      (1) An arterial systolic blood pressure of ≤ 90 mm Hg

      OR

      (2) A mean arterial pressure (MAP) ≤ 70 mm Hg for at least 1 hour despite adequate fluid resuscitation or adequate intravascular volume status

      OR

      (3) The need for vasopressors to maintain systolic blood pressure (SBP) ≥ 90 mm Hg or MAP ≥ 70 mm Hg

   b. RENAL

      Urine output < 0.5 mL/kg/hr for one hour, despite adequate fluid resuscitation

   c. RESPIRATORY

      $PaO_2/FiO_2 \leq 200$

   d. HEMATOLOGY

      Platelet count of < 80,000/mm^3 or a 50% decrease in the platelet count from the highest value recorded over the previous 3 days

   e. METABOLIC ACIDOSIS

      pH ≤ 7.30 or base deficit ≥ 5.0 mEq/L or a plasma lactate level > 1.5 times the upper limit of normal

AND

5. Patient has an Apache II score of greater than 25 and less than 53 (http://www.sfar.org/scores2/apache22.html). Do not delay treatment while gathering data to calculate the Apache II score as long as the patient meets the other criteria in this document. The Apache II score should be completed as soon as possible, however.

B. Contraindications:

In the following situations, the use of drotrecogin alfa (activated) is not recommended.

1. Active internal bleeding
2. Recent (within 3 months) hemorrhagic stroke
3. Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalization
4. Trauma patients with increased risk of life-threatening bleeding
5. Patients with an epidural catheter
6. Patients with intracranial neoplasm or mass lesion or evidence of cerebral herniation
7. Patients with known hypersensitivity to drotrecogin alfa (activated) or any component of the product
8. Life expectancy < 1 month or decision not to pursue aggressive medical care (*not in package insert; however, patients in this category were excluded from the pivotal study))*

C. Warnings

In the following conditions, the risks of administration should be weighed against the anticipated benefits.

1. Therapeutic heparin (≥ 15 units/kg/hr)
2. Platelet count < 30,000 X 10^6/L, even if the platelet count is increased after transfusions
3. Prothrombin time – INR > 3
4. Recent (within 6 weeks) gastrointestinal bleeding
5. Recent administration (within 3 days) of thrombolytic therapy
6. Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
7. Recent administration (within 7 days) of aspirin > 650mg per day or other platelet inhibitors
8. Recent (within 3 months) ischemic stroke
9. Patients with intracranial arteriovenous malformation or aneurysm
10. Known bleeding diathesis
11. Chronic sever hepatic disease
12. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location
13. For patients who are pregnant or breast-feeding, use only if clearly needed
14. Single organ dysfunction and recent surgery (within 30 days)

D. Exclusions from the Pivotal Study

Since some groups of patients were excluded from the clinical trial by Bernard, appropriateness of use in these patients must be determined on a case-by-case basis, as safety and efficacy data are not currently available. The following are the groups that were excluded from the clinical trial by Bernard:

1. Pregnant or breast-feeding patients
2. Age < 18 years or weight > 135 kg
3. Platelet count < 30,000/mm^3
4. Conditions that increased the risk of bleeding: surgery requiring general or spinal anesthesia within 12 hours before the infusion, the potential need for such surgery during the infusion, or evidence of active bleeding postoperatively; a history of severe head trauma requiring hospitalization, intracranial surgery, or stroke within 3 months before the study or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or mass lesions of the central nervous system; a history of congenital bleeding diatheses; gastrointestinal bleeding within 6 weeks before the study unless corrective surgery had been performed; and trauma considered to increase the risk of bleeding
5. Known hypercoagulable condition, including resistance to activated protein C; hereditary deficiency of protein C, protein S, or antithrombin III; presence of anticardiolipin antibody, antiphospholipid antibody, lupus anticoagulant, or homocysteinemia; or recently documented (within 3 months before the study) or highly suspected deep-vein thrombosis or pulmonary embolism
6. Patient's family, physician, or both not in favor of aggressive treatment of patient or presence of an advanced directive to withhold life-sustaining treatment
7. Patient not expected to survive 28 days because of uncorrectable medical condition, such as poorly controlled neoplasm or other end-stage disease
8. Moribund state in which death was perceived to be imminent
9. Human immunodeficiency virus infection in association with a last known CD4 count of ≤ 50/mm^3
10. History of bone marrow, lung, liver, pancreas, or small-bowel transplantation
11. Chronic renal failure requiring hemodialysis or peritoneal dialysis*
12. Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis, or chronic ascites
13. Acute pancreatitis with no established source of infection
14. Use of any of the following medications or treatment regimens: unfractionated heparin treatment for an active thrombotic event within 8 hours before the infusion †; low-molecular-weight heparin at a higher dose than recommended for prophylactic use (as specified in the package insert) within 12 hours before the infusion; warfarin (if used within 7 days before study entry and if the prothrombin time exceeded the upper limit of the normal range for the institution); acetylsalicylic acid at a dose of more than 650 mg/day within 3 days before the study; thrombolytic therapy within 3 days before the study ‡; glycoprotein IIb/IIIa antagonists within 7 days before study entry; antithrombin III at a dose of more

than 10,000 U within 12 hours before the study; or protein C within 24 hours before the study

* Acute renal failure was not an exclusion criterion

† Prophylactic treatment with a dose of unfractionated heparin of up to 15,000 U per day was permitted

‡ Thrombolytic agents were permitted for the treatment of thromboses within a catheter.

References:

1. Bernhard GR, Vincent JV, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Heltebrand JD, Ely W, and Fisher CJ, Jr., for the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J of Med*; 344(10):699-709, 2001.

2. Drotrecogin alfa (activated) package insert (http://pi.lilly.com/us/xigris.pdf).

3. Apache II score http://www.sfar.org/scores2/apache22.html.

4. Dhainaut JF, Laterre PF, Janes JM, Bernard GR, et al. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multi-organ dysfunction: data from the PROWESS trial. Intensive Care Med 2003; 29: 894-903.

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Pharmacy Benefits Management - Medical Advisory Panel

Criteria Checklist for Drotrecogin Alfa (activated)

CONTRAINDICATIONS	
1. Any of the following: ❑ Active internal bleeding ❑ Recent (within 3 months) hemorrhagic stroke ❑ Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalization ❑ Trauma with an increased risk of life-threatening bleeding ❑ Presence of an epidural catheter ❑ Intracranial neoplasm or mass lesion or evidence of cerebral herniation ❑ Known hypersensitivity to drotrecogin alfa (activated) or any component of the product ❑ Life expectancy < 1 month or decision not to pursue aggressive medical care (not in the package insert, however patients in this category were excluded from the pivotal study)	(1 or more?) ❑ yes ❑ no ***If yes, patient is* NOT *eligible to receive drotrecogin alfa***
SUSPECTED OR PROVEN INFECTION	
2. Patient has known or suspected infection defined as: ❑ Positive culture ❑ White cells in a normally sterile body fluid ❑ Perforated viscus ❑ Radiological and clinical evidence of pneumonia ❑ Other syndrome with high probability of infection (e.g., ascending cholangitis)	(1 or more?) ❑ yes ❑ no ***If no, patient is* NOT *eligible to receive drotrecogin alfa***
MONITORING	
3. Patient is receiving continuous monitoring in the intensive care unit	❑ yes ❑ no ***If no, patient is* NOT *eligible to receive drotrecogin alfa***
SIRS (MUST HAVE 3 OF THE 4 FOLLOWING CRITERIA)	
4. Pt has three or more signs of SIRS as defined as: ❑ Core temp of ≥ 100.4 F (38°C) or ≤ 96.8 F (36°C) ❑ HR of ≥90 beats/minute ❑ RR ≥ 20 breaths/min or $PaCO_2$ ≤ 32 mmHg or mechanical ventilation for acute (not chronic) respiratory process ❑ WBC ≥ 12,000/mm^3 or ≤ 4,000/mm^3 or ≥ 10% immature neutrophils	(3 or more?) ❑ yes ❑ no ***If no, patient is* NOT *eligible to receive drotrecogin alfa***
ORGAN SYSTEM DYSFUNCTION	
5. Dysfunction of 2 or more organs or systems defined as: ❑ CARDIOVASCULAR: Arterial systolic BP ≤ 90mmHg **OR** a mean arterial pressure (MAP) ≤70mmHg for at least 1 hour despite adequate fluid resuscitation or adequate intravascular volume status, **OR** the need for vasopressors to maintain systolic blood pressure (SBP) ≥ 90 mm HG or MAP ≥ 70 mm Hg ❑ RENAL: Urine output < 0.5 ml/kg/hr for > 1 hour, despite adequate fluid resuscitation ❑ RESPIRATORY: PaO_2/FiO_2 ≤ 200 ❑ HEMATOLOGIC: Platelet count < 80,000/mm^3 or decreased by 50% from highest value in the previous 72 hours ❑ METABOLIC: PH ≤ 7.30 or base deficit ≥ 5 mEq/L with plasma lactate > 1.5 times the upper limit of normal	(2 or more?) ❑ yes ❑ no ***If no, patient is* NOT *eligible to receive drotrecogin alfa***

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APACHE II	
6. APACHE II ≥ 25 and < 53 as calculated on basis of physiologic and laboratory data obtained within the immediately preceding 24 hour period (http://www.sfar.org/scores2/scores2.html). Treatment need not be delayed while gathering data to calculate the APACHE II score as long as the patient meets the other criteria, however, the APACHE II score must be completed as soon as possible.	❑ yes ❑ no
ACUITY	
7. Less than 48 hours after the onset of the first sepsis induced organ dysfunction	❑ yes ❑ no
WARNINGS: According to the package insert, the increased risk of bleeding should be carefully considered when deciding whether to use drotrecogin therapy for patients with one or more of the following conditions.	
The following conditions led to exclusion from the phase III trial: • Concurrent therapeutic heparin (greater than or equal to 15 units/kg/hr) • Platelet count <30,000, even if the platelet count is increased after transfusions • Prothrombin time-INR >3.0 • Recent (within 6 weeks) gastrointestinal bleeding (unless corrective surgery had been performed) • Recent administration (within 3 days) of thrombolytic therapy (except for treatment of thrombosed catheters) • Recent administration (within 7 days) of aspirin or glycoprotein IIb/IIIa inhibitors • Recent (within 3 months) ischemic stroke (**see contraindications)** • Intracranial arterio-venous malformation or aneurysm • Known bleeding diathesis • Chronic severe hepatic disease (portal hypertension, cirrhosis, chronic jaundice or ascites) ***The following did not lead to exclusion from the phase III trial:*** • Recent administration (within 7 days) of oral anticoagulants or platelet inhibitors other than aspirin • Any other condition in which bleeding is a significant hazard or would be particularly difficult to manage	
Other warnings	
In patients with single organ dysfunction and recent surgery (within 30 days), all-cause mortality was higher in patients receiving drotrecogin compared to the placebo group.	
OTHER CAUTIONS: The effectiveness of drotrecogin has not been established in patients with the following conditions, all of which led to exclusion from the phase 3 trial.	
• Age < 18 years or weight > 135 kg (298 pounds) • Recent administration (within 12 hours) of greater than 10,000 U of antithrombin III • Patients who are pregnant or breastfeeding • Surgery requiring general or spinal anesthesia within the preceding 12 hours, active post-operative bleeding, intra-cranial surgery within 3 months, or anticipated surgery requiring general or spinal anesthesia during the infusion • Trauma considered to increase the risk of bleeding • Hypercoagulable condition • Highly suspected deep venous thrombosis or pulmonary embolism • Acute pancreatitis with no established source of infection • HIV+ with ≤ 50 $CD4^+$ cells or status-post bone marrow, lung, liver, pancreas or small bowel transplant • Chronic renal failure requiring hemodialysis or peritoneal dialysis (acute renal failure was not an exclusion) • Recent (within 3 months) documented or highly suspected DVT or pulmonary embolism	
Patient meets ***all*** inclusion criteria and does not have any contraindications	❑ yes ❑ no

Approved by Physician: _____ Date/time: _____
(Must be a critical care fellow or an
infectious diseases / critical care / pulmonary attending)

Patient name (& last 4 digits of SSN): _____ Reviewer: _____

□ APPROVED □ NOT APPROVED

CLINICAL STUDIES

The efficacy of Drotrecogin was studied in an international, multi-center, randomized, double-blind, placebo-controlled trial of 1690 patients with severe sepsis. Entry criteria included a systemic inflammatory response presumed due to infection and at least one associated acute organ dysfunction. Acute organ dysfunction was defined as one of the following: cardiovascular dysfunction (shock, hypotension, or the need for vasopressor support despite adequate fluid resuscitation); respiratory dysfunction (relative hypoxemia (PaO_2/FiO_2 ratio <250)); renal dysfunction (oliguria despite adequate fluid resuscitation); thrombocytopenia (platelet count < 80,000/mm3 or 50% decrease from the highest value the previous 3 days); or metabolic acidosis with elevated lactic acid concentrations. Patients received a 96 hour infusion of Drotrecogin at 24 µg/kg/hr or placebo starting within 48 hours after the onset of the first sepsis induced organ dysfunction. Exclusion criteria encompassed patients at high risk for bleeding (*see* **CONTRAINDICATIONS** and **WARNINGS**), patients who were not expected to survive for 28 days due to a pre-existing, non-sepsis related medical condition. The primary efficacy endpoint was all-cause mortality assessed 28 days after the start of study drug administration. Prospectively defined subsets for mortality analyses included groups defined by APACHE II Score. The APACHE II score was calculated from physiologic and laboratory data obtained within the 24-hour period immediately preceding the start of study drug administration irrespective of the preceding length of stay in the Intensive Care Unit. Baseline APACHE II score was correlated with risk of death; among patients receiving placebo, those with the lowest APACHE II scores had a 12% mortality rate, while those in the 2nd, 3rd, and 4th APACHE quartiles had mortality rates of 26%, 36% and 49%, respectively. The observed mortality difference between Drotrecogin and placebo was limited to the half of patients with higher risk of death, i.e., APACHE II score =25, the 3rd and 4th quartile APACHE II scores (Table 1). The efficacy of Drotrecogin has not been established in patients with lower risk of death, e.g., APACHE II score < 25.

Table : 28-Day All-Cause Mortality for All Patients and for Subgroups Defined by APACHE II Score

	Drotrecogin **N (mortality%)**	**Placebo** **N (mortality%)**	**Absolute mortality difference (%)**	**Relative Risk (RR)**	**95% CI for RR**
Overall	850 (25%)	840 (31%)	-6	0.81	0.70 – 0.93
APACHE II quartile (score)					
$1^{st} + 2^{nd}$ (3 – 24)	436 (19%)	437 (19%)	0	0.99	0.75 – 1.30
3^{rd} and 4^{th} (25 – 53)	414 (31%)	403 (44%)	-13	0.71	0.59 – 0.85

CONTRAINDICATIONS and **WARNINGS** (see front page for contra-indications and additional warnings)

Bleeding is the most common serious adverse effect associated with Drotrecogin therapy. Each patient being considered for therapy with Drotrecogin should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Should clinically important bleeding occur, immediately stop the infusion of Drotrecogin. Continued use of other agents affecting the coagulation system should be carefully assessed. Once adequate hemostasis has been achieved, continued use of Drotrecogin may be reconsidered. Drotrecogin should be discontinued 2 hours prior to undergoing an invasive surgical procedure or procedures with an inherent risk of bleeding. Once adequate hemostasis has been achieved, initiation of Drotrecogin may be reconsidered 12 hours after major invasive procedures or surgery or restarted immediately after uncomplicated less invasive procedures.

In a separate analysis of the PROWESS data, all-cause mortality was higher with drotrecogin in patients with single organ dysfunction and recent surgery (within 30 days) compared to placebo. For drotrecogin, the 28-day and in-hospital mortality was 10/49 (20.4%) and 14/48 (29.2%) respectively compared to 8/49 (16.3%) and 8/47 (17.0%) respectively for the placebo group. The higher risk of all-cause mortality was also seen in a preliminary analysis of results from the ADDRESS study. In the subgroup with single organ dysfunction AND recent surgery, the 28-day and in-hospital mortality rate was 67/323 (20.7%) and 76/325 (23.4%) respectively in the drotrecogin group compared to 44/313 (14.1%) and 62/314(19.8%) respectively the placebo group.

PRECAUTIONS

Laboratory Tests

Most patients with severe sepsis have a coagulopathy that is commonly associated with prolongation of the activated partial thromboplastin time (APTT) and the prothrombin time (PT). Drotrecogin may variably prolong the APTT. Therefore, the APTT cannot be reliably used to assess the status of the coagulopathy during Drotrecogin infusion. Drotrecogin has minimal effect on the PT and the PT can be used to monitor the status of the coagulopathy in these patients.

FURTHER DETAILS

More details regarding drotrecogin are available in the presentation to the FDA Advisory Board (see http://www.fda.gov/ohrms/dockets/ac/01/slides/3797s1_01_Lilly-CORE/ and http://www.fda.gov/ohrms/dockets/ac/01/slides/3797s1_02_Forsyth/) and the formula for calculating APACHE II scores (http://www.sfar.org/scores2/scores2.html).

The criteria checklist was initially prepared by VISN 22 and Greater Los Angeles VA Medical Center clinical staff. The VHA Infectious Diseases Program Office, Pulmonary & Critical Care Field Advisory Group, and Pharmacy Benefits Management - Medical Advisory Panel clinical staff assisted in its review.